6.11 SACUBITRIL with VALSARTAN, Tablet containing sacubitril 24.3 mg + valsartan 25.7 mg, Tablet containing sacubitril 48.6 mg + valsartan 51.4 mg, Tablet containing sacubitril 97.2 mg + valsartan 102.8 mg, Entresto®, Novartis Pharmaceuticals Australia Pty Ltd

1 Purpose of submission

1.1 The submission requested an extension to the existing Authority Required (Streamlined) listing for sacubitril/valsartan fixed dose combination (FDC) for the treatment of chronic heart failure with reduced ejection fraction. The extended listing would allow patients to initiate treatment with sacubitril/valsartan without first requiring treatment with an angiotensin II converting enzyme (ACE) inhibitor, angiotensin II receptor blocker (ARB), or a beta-blocker, and change the degree of reduced left ventricular ejection fraction (LVEF) required from ≤40% to <50%.

1.2 Listing was requested on the basis of acceptance that the cost effectiveness of sacubitril/valsartan versus enalapril (as proxy for all ACE-inhibitors) in the expanded population is unchanged from the current PBS population.

Table 1: Key components of the clinical issue addressed in the submission

Component	Description
Population	Patients with chronic heart failure and reduced LVEF of <u>≤50%,</u> with or <u>without</u> prior stabilisation <u>on ACE-inhibitors or ARBs.</u>
Intervention	Sacubitril/valsartan fixed dose combination, initiated at low dose and titrated to target dose
Comparator	Enalapril 20 mg, as a proxy for all ACE-inhibitors
Outcomes	Cardiovascular death, heart failure hospitalisation/re-hospitalisation, requirement of LVAD, listing for cardiac transplant.
Clinical claim	In patients with heart failure with reduced ejection fraction, sacubitril/valsartan is more effective than ACE-inhibitors (represented by enalapril) in reducing cardiovascular mortality and heart failure hospitalisations; and has similar safety to enalapril.

Source: Table P1, pp17-18; Section 2, p29 of the submission.
Abbreviations: ACE, angiotensin II converting enzyme , ARB, angiotensin II receptor blocker; HF, heart failure; LVAD, left ventricular assist device; LVEF, left ventricular ejection fraction.
<u>Underlining</u> denotes changes to population with proposed extension to the PBS restriction.

2 Background

Registration status

2.1 Sacubitril/valsartan was listed on the Australian Register of Therapeutic Goods (ARTG) on 20 January 2016 for the following indication: for use in adult patients for the treatment of chronic heart failure (NYHA Class II-IV) with reduced ejection fraction. TGA documentation was not provided with the submission.

Previous PBAC consideration

2.2 Sacubitril/valsartan was listed on the PBS in June 2017 following consideration by the PBAC in March, July and August 2016, for patients with heart failure with LVEF ≤ 40%, NHYA class II-IV, and receiving concomitant optimal standard chronic heart failure treatment including the maximum tolerated dose of a beta-blocker, and stabilised on an ACE-inhibitor or ARB at the time of treatment initiation with sacubitril/valsartan. The recommendation was made on the basis of acceptable cost effectiveness compared to enalapril, with key clinical evidence presented from the PARADIGM-HF trial, which was a head-to-head randomised trial comparing sacubitril/valsartan to enalapril in patients with LVEF ≤40% (changed to LVEF ≤35% after early protocol amendment) over a median follow-up period of 27 months. The primary outcome of this trial was a composite of death from cardiovascular causes or hospitalisation for heart failure.

3 Requested listing

3.1 The submission's proposed changes to the current PBS restriction are presented below. Deletions are in ~~strikethrough~~ and additions are in **bold**.

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
SACUBITRIL/VALSARTAN Tablet, 24 mg/26 mg, 49 mg/51 mg, 97 mg/103 mg, 56	1	5	*$202.89* published price $[redacted] effective price	Entresto ® Novartis Pharmaceuticals

Category/Program:	General Schedule
PBS indication:	Heart failure with reduced ejection fraction (HF-rEF)
Treatment phase:	Initial and continuing
Restriction:	Streamlined Authority
Clinical criteria:	Patient must be symptomatic with NYHA classes II, III or IV, AND Patient must have a documented left ventricular ejection fraction (LVEF) of less than ~~or equal to 40%~~ **50%**, AND Patient must receive concomitant optimal standard chronic heart failure treatment~~, which must include the maximum tolerated dose of a beta-blocker, unless contraindicated or not tolerated,~~. **A beta-blocker is usually commenced following the introduction of an ACE-I, ARB or ARNI, but can be commenced before if euvolaemic. Up-titration should not be to the detriment of starting other drugs that have been shown to be effective in HF.** ~~AND~~ ~~Patient must have been stabilised on an ACE inhibitor at the time of initiation with this drug, unless such treatment is contraindicated according to the TGA-approved Product Information or cannot be tolerated; OR~~ ~~Patient must have been stabilised on an angiotensin II blocker at the time of initiation with this drug, unless such treatment is contraindicated according to the TGA-approved Product Information or cannot be tolerated,~~ AND The treatment must not be co-administered with an ACE inhibitor or an angiotensin II blocker.
Prescriber criteria:	~~Continuing Therapy Only:~~ ~~For prescribing by nurse practitioners as continuing therapy only, where the treatment of, and prescribing of medicine for, a patient has been initiated by a medical practitioner.~~ **Nurse prescribing (Shared Care Model):** **For prescribing by nurse practitioners where care of a patient is shared between a nurse practitioner and medical practitioner in a formalised arrangement with an agreed management plan.** Further information can be found in the Explanatory Notes for Nurse Practitioners

Source: Table 1.4, p26; Table 1.5, pp26-27 of the submission.

Note: The DPMQ used in the submission did not take into account changes to dispensing fees and pharmacy mark-ups at 1 July 2020. During the evaluation, the DPMQ (published: $198.25; effective: $[redacted]) for sacubitril/valsartan was updated and relevant costs re-calculated.

3.2 A special pricing arrangement is already in place for sacubitril/valsartan, and the submission's requested expansion to the PBS listing would also form part of this special pricing arrangement, with the same effective price (with adjustments for recent increases in dispensing fees and pharmacy mark-ups on 1 July 2020).

3.3 The submission stated that the requested changes to the PBS restrictions are in line with the Cardiac Society of Australian and New Zealand (CSANZ) clinical practice guidelines (updated in 2018), and that these changes address potential delays in accessing sacubitril/valsartan, with a less restricted PBS listing reducing barriers to

access. Clinical evidence presented in this submission to support the changes to the restriction was limited to subgroup comparisons of ACE-inhibitor/ARB-naïve and -experienced patients. There was no evidence presented supporting the change of LVEF thresholds, nor the removal of requirement for maximal doses of beta-blockers prior to treatment with sacubitril/valsartan.

3.4 The ESC noted no evidence was presented to support the submission's claim that the cost effectiveness of sacubitril/valsartan in the LVEF 40%-49% population would be the same as the LVEF ≤40% population. The ESC considered this assumption was highly implausible as this new population was likely to have milder heart failure (LVEF 40-50%) and have a lower risk of adverse outcomes (death or hospitalisation for heart failure).

3.5 The submission noted that the updated CSANZ guidelines for the use of sacubitril/valsartan reflect the restrictions specified in the current PBS listing, and therefore specifies use in patients with LVEF ≤40%, despite receiving maximally tolerated or target doses of an ACE inhibitor (or ARB) and a beta-blocker (unless contraindicated). The submission's clinical management algorithm, based on these guidelines, does not capture those patients for whom management would change with the proposed expansion of the current PBS listing. The ESC noted no direct evidence was presented to support the requested change to remove the requirement that patients be on maximum tolerated dose of a beta-blocker. However, the ESC also agreed with the submission that titration of a beta-blocker to maximum tolerated dose can delay optimisation of treatment, and considered it was reasonable that the listing of sacubitril/valsartan be more flexible with regards to dosing requirements for beta-blockers.

3.6 The proposed criterion detailing beta-blocker commencement relates to the treatment algorithm in clinical guidelines and does not explicitly outline requirements for PBS eligibility. The Pre-PBAC Response advocated that the proposed change to the beta blocker requirement was consistent with CSANZ guidelines which state the sequence of drug(s) is less important than the final regimen. The PBAC agreed with the Pre-PBAC Response and considered it was appropriate to allow for greater flexibility for individual prescriber decision making with regards to beta blocker use and dosing in the sacubitril/valsartan listing.

3.7 The proposed PBS restriction allows for treatment with sacubitril/valsartan in patients that would have otherwise been adequately managed on earlier, less costly, lines of therapy (ACE inhibitor/ARB and beta-blocker, with or without a mineralocorticoid receptor antagonist).

3.8 The change to nurse prescribing allowing for initiation by a nurse practitioner is not in line with the TGA Product Information, which states that treatment should be initiated, and up-titration conducted, by a physician experienced with the treatment of heart failure. The ESC considered it may be reasonable to allow nurse practitioners

to prescribe sacubitril/valsartan for continuing therapy and during dose titration, however did not consider it was appropriate for nurse practitioners to initiate therapy.

For more detail on PBAC's view, see section 7 PBAC outcome.

4 Population and disease

4.1 Chronic heart failure is a complex clinical syndrome characterised by symptoms such as dyspnoea, peripheral oedema and fatigue, caused by an underlying structural and/or functional cardiac abnormality that impairs the ability of the heart ventricle to fill with or eject blood. Reduction in cardiac output leads to the activation of compensatory mechanisms, including the release of cardiac mediators, over-activation of the sympathetic nervous system and renin-angiotensin-aldosterone systems (resulting in increased heart rate, increased blood pressure, and salt and fluid retention), inflammation and myocardial remodelling. Heart failure is commonly classified based on the left ventricular ejection fraction. Heart failure with reduced ejection fraction refers to symptoms with or without signs of heart failure and an LVEF ≤40%. Heart failure with preserved ejection fraction (HFpEF) is defined as clinical symptoms with or without signs of heart failure, an LVEF ≥50%, and objective evidence of either relevant structural heart disease or diastolic dysfunction without an alternative cause (e.g., significant valvular heart disease). If LVEF is mildly reduced (41–49%), additional criteria are required (signs of heart failure, diastolic dysfunction with high filling pressure demonstrated by invasive means or echocardiography or biomarker testing).

4.2 The submission requested a broadening of the existing population (heart failure with reduced LVEF ≤40% and stabilised on ACE-inhibitor or ARB and maximum tolerated dose of a beta-blocker), to include all patients with heart failure with reduced ejection fraction by including these additional groups: patients with LVEF between 41% and 49%, and patients not previously stabilised on an ACE-inhibitor/ARB or on maximum beta-blocker dose. The proposed changes to the PBS restriction move sacubitril/valsartan to first line therapy and would permit use in an expanded population with less severe disease. There is potential for sacubitril/valsartan to be used in patients who would have otherwise been adequately managed with an ACE-inhibitor/ARB (NYHA Class I). Initiating sacubitril/valsartan without first titrating a beta-blocker to the maximum tolerated dose may reduce the number of patients receiving the maximum dose of a beta-blocker.

4.3 Sacubitril/valsartan FDC is comprised of an ARB (valsartan), and an angiotensin-receptor neprilysin inhibitor (ARNI, sacubitril). Valsartan acts by blocking the action of angiotensin II, leading to vasodilation and reduced blood pressure. Sacubitril inhibits neprilysin, which also promotes vasodilation, natriuresis and diuresis, increased glomerular filtration rate and renal blood flow, inhibition of renin and aldosterone release, reduction of sympathetic activity and anti-hypertrophic and anti-fibrotic

effects. Neprilysin inhibition alone has not demonstrated clinically meaningful reductions in blood pressure, thus sacubitril is only available in combination with valsartan. Sacubitril must not be combined with an ACE inhibitor as this combination was associated with serious angioedema in clinical trials.

For more detail on PBAC's view, see section 7 PBAC outcome.

5 Comparator

5.1 The submission nominated enalapril (as a proxy for all ACE-inhibitors) as the main comparator. The main arguments provided in support of this nomination were that enalapril was accepted as the main comparator in the previous PBAC considerations of sacubitril/valsartan in March, July and August 2016; and it is the comparator in the key clinical trial included in this submission (PIONEER-HF). This was appropriate.

5.2 The submission stated that ARBs were also considered to be key secondary comparators in the previous PBAC consideration. No evidence of comparative efficacy with stand-alone ARB therapy was presented in this submission.

5.3 Dapagliflozin is being considered for listing for the treatment of heart failure with reduced ejection fraction at this same meeting.

For more detail on PBAC's view, see section 7 PBAC outcome.

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer comments

6.2 The PBAC noted that no consumer comments were received for this item.

Clinical trials

6.3 The submission was based on:

- one head-to-head randomised trial comparing sacubitril/valsartan to enalapril (PIONEER-HF);
- a pre-specified subgroup analysis of efficacy in ACE-inhibitor/ARB-naïve and experienced patients from the PIONEER-HF trial;
- a randomised safety study of sacubitril/valsartan administered either pre- or post-hospital discharge, with subgroup analysis in ACE-inhibitor/ARB-naïve and experienced patients (TRANSITION); and
- a supplementary *observational* study comparing the efficacy of treatment with sacubitril/valsartan and enalapril in a retrospective cohort analysis, with a

subgroup analysis of patients with or without previous ACE-inhibitor/ARB treatment (Tan 2020).

These studies were published after the previous consideration of sacubitril/valsartan (which was based on data from PARADIGM-HF) and have not been previously considered by the PBAC. The submission did not provide evidence in support of extending the current sacubitril/valsartan restriction for patients with LVEF 41%-49%.

6.4 Details of the studies presented in the submission are provided in the table below. The clinical trial reports for the included studies were not provided with the submission, nor were they provided following a request to the sponsor during the evaluation. The absence of this data means that the evaluation was necessarily more limited and verification was more limited. The ESC noted that the PBAC would need to take this into consideration when making a determination of the submission.

Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
PIONEER HF	Velazquez EJ, Morrow DA et al. Angiotensin-neprilysin inhibition in acute decompensated heart failure. Ambrosy AP et al. Angiotensin receptor-neprilysin inhibition in acute decompensated heart failure based on prior exposure to a conventional renin-angiotensin system antagonist. A prespecified subgroup analysis of the PIONEER-HF trial. Morrow DA, Velazquez EJ et al. Clinical outcomes in patients with acute decompensated heart failure randomly assigned to sacubitril/valsartan or enalapril in the PIONEER-HF trial.	*NEJM* 2019; 380:539-548 Presented at American College of Cardiology Annual Meeting 2019; March 16-18, New Orleans. *Circulation* 2019; 139(19):2285-2288
TRANSITION	Wachter R et al. Initiation of sacubitril/valsartan in haemodynamically stabilised heart failure patients in hospital or early after discharge: Primary results of the randomised TRANSITION study.	*Eur J Heart Fail* 2019; 21(8):998-1007
Tan 2020	Tan NY, Sangaralingham LR et al. Comparative effectiveness of sacubitril-valsartan versus ACE/ARB therapy in heart failure with reduced ejection fraction.	*JACC: Heart Failure* 2020; 8(1):43-54

Source: Created during the evaluation from publications cited in Section 2 pp29-30 of the submission.

6.5 The key features of the included evidence are summarised in the table below.

Table 3: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Key Outcomes
PIONEER-HF	887	Phase 3b/4 multicentre, double blind, active controlled, parallel group RCT (8 weeks)	*Low*	Adults hospitalised with primary diagnosis of acute decompensated HF, LVEF≤40%	Change from baseline in NT-proBNP concentration, death, rehospitalisation for heart failure, implantation of LVAD, inclusion on heart transplant list
TRANSITION	1002	Phase 4, multicentre, open-label, parallel group randomised controlled safety and biomarker study (10 weeks)	*High*	Adults hospitalised with acute decompensated HF (new or exacerbation of chronic HF), LVEF≤40%, NYHA Class II-IV	% patients achieving target sacubitril/valsartan dose of 97/103mg twice daily at the end of week 10 after randomisation; adverse events
Tan 2020	15,786	Retrospective cohort matched-pairs study of medical claims data (approx. 2.5 years)	*High*	Adults with prior diagnosis of systolic heart failure, LVEF <45%.	Composite outcome of all-cause-mortality or all-cause hospitalisation

Source: Section 2.1, pp30-32; Section 2.2.3, pp43-44 of the submission; PIONEER-HF and TRANSITION publications.
Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; HF, heart failure; LVAD, left ventricular assist device; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro b-type natriuretic peptide; NYHA, New York Heart Association; RCT, randomised controlled trial

6.6 The PIONEER-HR trial compared 8 weeks of treatment with sacubitril/valsartan or enalapril in patients hospitalised with acute decompensated heart failure, with LVEF ≤40%. The trial included pre-specified subgroup comparisons of ACE-inhibitor/ARB-naïve and -experienced patients. Patients in the treatment-experienced subgroup were older, more likely to have a prior diagnosis of heart failure before the index hospitalisation date, and were more likely to be receiving other treatments for heart failure compared to the ACE-inhibitor/ARB-naïve subgroup). Clinical endpoints in the PIONEER-HF trial were exploratory only, while results were not adjusted for multiple comparisons. Data for the subgroup analysis were obtained from a conference poster, and limited information was available for the subgroup analysis methodology. The Pre-Sub-Committee Response (PSCR) stated that no further data on the subgroup analysis would be forthcoming. The ESC felt that this was inappropriate and greatly limited the weight that could be placed on this data. However, the pre-PBAC response did include a reference to this analysis being subsequently published in the Journal of the American College of Cardiology (Ambrosy, 2020).

6.7 The TRANSITION trial compared initiation of sacubitril/valsartan in patients either pre- or post-discharge from hospitalisation for acute decompensated heart failure. Results from this study were included in the submission to compare safety outcomes in ACE-inhibitor/ARB-naïve or experienced patients.

6.8 The retrospective cohort study (Tan 2020) used prescribing claims data from a US database for sacubitril/valsartan or an ACE-inhibitor/ARB, in patients with a diagnosis of heart failure. Patients were matched based on clinical characteristics and prior treatments, and subgroup results were available based on ACE-inhibitor/ARB experience.

6.9 To support the requested change to the PBS restriction to allow initiation of sacubitril/valsartan prior to maximal doses of a beta-blocker the submission briefly described the results of an open-label, blinded-endpoint study (CIBIS III) that compared initiation of treatment with a beta-blocker (bisoprolol 1.25 mg daily titrated to 10 mg daily for 6 months) followed by addition of an ACE-inhibitor (enalapril 2.5 mg twice daily titrated to 10 mg twice daily for 6-24 months), or the reverse. The CIBIS III study included clinically-stable adults aged at least 65 years, with NYHA class II or III, and LVEF ≤35%.

6.10 The submission stated that there were no published data available for treatment of patients with LVEF between 41% and 49%. During the evaluation, a published pooled analysis was found (Solomon 2020), that combined 8399 randomised patients from the key sacubitril/valsartan versus enalapril clinical trial (PARADIGM-HF) with 4796 patients from PARAGON-HF, a similarly-designed study of sacubitril/valsartan versus valsartan, which recruited patients with LVEF of 45% or greater. Although these results do not precisely match the expanded restriction, the ESC noting that the PARAGON-HF trial targeted a patient population with HFpEF, they are currently the best available evidence in this subgroup.

6.11 The ESC noted the submission did not provide a literature search or clinical study reports, and that other information generally required for a major submission was missing. This greatly impeded the Sub-Committee's ability to formulate advice for the PBAC. Furthermore, the ESC considered that the evidence presented was of limited applicability to the requested expanded listing and relied heavily on subgroup analyses which had not been adjusted for multiple comparisons. As such, the ESC considered the submission was largely uninformative for decision-making.

Comparative effectiveness

Whole trial results

6.12 The primary outcome of the PIONEER-HF trial was time averaged proportional change in N-terminal pro b-type Natriuretic Peptide (NT-proBNP) from baseline to weeks 4 and 8. NT-proBNP is a surrogate outcome for clinical outcomes in heart failure, whereby reductions in NT-proBNP have been associated with a lower risk of CV mortality or hospitalisation for worsening heart failure. Sacubitril/valsartan was associated with a statistically significantly greater reduction in NT-proBNP compared with enalapril (see table below).

Table 4: Results of change from baseline in NT-proBNP – PIONEER-HF whole trial population

	Sacubitril/valsartan N=440	Enalapril N=441	Ratio of change (95% CI)
% change	-46.7%	-25.3%	0.71 (0.63,0.81)

Source: Section 2.2.1, p35 of the submission
Abbreviations: NT-proBNP, N-terminal pro b-type natriuretic peptide

6.13 Results of the exploratory clinical outcomes for the whole trial population of PIONEER-HF are presented in the table below.

Table 5: Results of exploratory clinical outcomes – PIONEER-HF whole trial population

Outcome, n (%)	Sacubitril/valsartan N=440	Enalapril N=441	Hazard ratio (95% CI)
Composite of clinical events	249 (56.6)	264 (59.9)	0.93 (0.78, 1.10)
Death	10 (2.3)	15 (3.4)	0.66 (0.30, 1.48)
Rehospitalisation for heart failure	35 (8.0)	61 (13.8)	**0.56 (0.37, 0.84)**
Implantation of LVAD	1 (0.2)	1 (0.2)	0.99 (0.06, 15.97)
Inclusion on heart transplant list	0	0	NA
Unplanned outpatient visit – IV diuretics	2 (0.5)	2 (0.5)	1.00 (0.14, 7.07)
Additional heart failure drug	78 (17.7)	84 (19.0)	0.92 (0.67, 1.25)
Increase diuretic dose >50%	218 (49.5)	222 (50.3)	0.98 (0.81, 1.18)
Composite of serious clinical events (death, rehospitalisation for heart failure, LVAD implant, inclusion on heart transplant list)	41 (9.3)	74 (16.8)	**0.54 (0.37, 0.79)**
Post-hoc composite outcome (cardiovascular death or rehospitalisation for heart failure)	NR (9.2)	NR (15.2)	**0.58 (0.39-0.87)**

Source: Figure 2.4, p36 of the submission

Abbreviations: CI, confidence interval; LVAD, left ventricular assist device; n, number of participants with event; N, total participants in group. Bold indicates statistically significant results.

6.14 There was no statistically significant difference between sacubitril/valsartan and enalapril for the composite endpoint of clinical events, but there were statistically significant differences reported for the composite outcome of serious clinical events, for the post hoc composite outcome of cardiovascular death or rehospitalisation for heart failure, and for rehospitalisation for heart failure. Results for clinical outcomes in the PIONEER-HF trial should be interpreted with caution, given they are exploratory outcomes that have not been adjusted for multiple comparisons.

6.15 The submission claimed that the whole-trial results for the post-hoc composite outcome of cardiovascular death or rehospitalisation for heart failure from the PIONEER-HF trial (HR 0.58, 95% CI 0.39-0.87) were consistent with results for the same outcome previously observed in the PARADIGM-HF trial (HR 0.80, 95% CI 0.73, 0.87). The patient populations and treatment durations in these trials were different (PIONEER-HF subjects were hospitalised with acute heart failure, treatment duration 8 weeks; while PARADIGM-HF patients were not required to be hospitalised, median treatment duration 27 months), limiting the comparability of these results.

6.16 Results from the retrospective cohort study (Tan 2020) for the primary composite outcome of all-cause mortality or all-cause hospitalisation are presented in the table below. The submission noted that all-cause hospitalisations were used as the primary outcome to avoid any discrepancies in hospital coding.

Table 6: Key clinical outcomes from retrospective matched cohort study (Tan 2020), all matched patients

Outcome	Sacubitril/valsartan N=7893		ACE-inhibitor/ARB N=7893		Hazard ratio (95% CI)
	n (%)	Per 100 pt yrs	n (%)	Per 100 pt yrs	
All-cause mortality or hospitalisation	1764 (22.3)	51.74	2110 (26.7)	60.12	**0.86 (0.81, 0.91)**
All-cause hospitalisation	1716 (21.8)	50.30	2060 (26.1)	58.66	**0.86 (0.80, 0.91)**
All-cause mortality	170 (2.2)	4.31	229 (2.9)	5.36	**0.80 (0.65, 0.97)**
Heart failure hospitalisation	646 (17.2)	17.16	648 (15.9)	15.93	1.07 (0.96, 1.19)

Source: Figures 1-4, Tan 2020 publication

Abbreviations: ARB, angiotensin II receptor blocker; CI, confidence interval; HR, hazard ratio; Per 100 pt yrs, event rate per 100 patient-years

6.17 Compared to ACE-inhibitors/ARBs, sacubitril/valsartan was associated with a lower risk of all-cause mortality or hospitalisation, or a composite of both outcomes, for the whole study matched population. However, there was no difference between treatment groups for heart failure hospitalisation. The authors argued that the use of codes to identify heart failure hospitalisation had previously been identified as problematic and may have contributed to these findings. Results should be interpreted with caution given the observational nature of the study.

6.18 The submission claimed that the study results for the composite outcome of all-cause death or all-cause hospitalisation from Tan (2020) (HR 0.81, 95% CI 0.81, 0.91) were consistent with results for the composite outcome of cardiovascular death or rehospitalisation for heart failure previously observed in the PARADIGM-HF trial (HR 0.80, 95% CI 0.73, 0.87). The outcomes assessed in these studies were different and results cannot be compared.

6.19 No quality of life or functional outcomes were reported in any of the included studies.

Subgroup analyses to inform ACE-inhibitor/ARB-naïve population

6.20 The submission provided results from a pre-specified subgroup analysis from the PIONEER-HF trial, comparing treatments groups based on prior use of ACE-inhibitors/ARBs, aligning the trial population with one of the requested expansions to current PBS restrictions. The complement to this subgroup would be eligible for treatment with sacubitril/valsartan based on the current restriction.

Table 7: Pre-specified subgroup analysis of exploratory clinical outcomes – PIONEER-HF

Outcome (n, %)	ACE-inhibitor/ARB-naive			ACE-inhibitor/ARB experienced		
	Sacubitril/ valsartan N=232	Enalapril N=227	HR (95% CI)	Sacubitril/ valsartan N=208	Enalapril N=214	HR (95% CI)
Death	4 (1.7)	7 (3.1)	0.54 (0.16, 1.85)	6 (2.9)	8 (3.7)	0.80 (0.28, 2.29)
HF rehospitalisation	**14 (6.0)**	**25 (11.0)**	**0.52 (0.27, 0.99)**	21 (10.1)	36 (16.8)	0.60 (0.35, 1.03)
LVAD implantation	0 (0)	1 (0.4)	NA	1 (0.5)	0 (0)	NA
Cardiac transplant	0 (0)	0 (0)	NA	0 (0)	0 (0)	NA
Composite of serious clinical events	**17 (7.3)**	**30 (13.2)**	**0.52 (0.29, 0.95)**	**24 (11.5)**	**44 (20.6)**	**0.56 (0.34, 0.93)**

Source: Figure 2.8, p39 of the submission.
Abbreviations: ACE, angiotensin converting enzyme; ARB, angiotensin II receptor blocker; CI, confidence interval; HF, heart failure; LVAD, left ventricular assist device

6.21 For the composite outcome of serious clinical events (death, heart failure rehospitalisation, LVAD implantation, cardiac transplantation), there were statistically significant differences in favour of sacubitril/valsartan over enalapril in both the ACE-inhibitor/ARB-naïve and -experienced subgroups. The study authors stated that confidence intervals were not adjusted for multiple comparisons. The relative magnitude of the difference between treatments for both subgroups was consistent with the whole trial results. However, these results should be interpreted with caution due to heterogeneity between subgroup populations (patients in the treatment-experienced subgroup were older, more likely to have a prior diagnosis of heart failure before the index hospitalisation date, and were more likely to be receiving other treatments for heart failure compared to the ACE-inhibitor/ARB-naïve subgroup), and a lack of available results of any testing for treatment interaction.

6.22 The retrospective cohort study (Tan 2020) also presented a subgroup analyses for ACE-inhibitor/ARB-naïve or -experienced subgroups. The study found similar relative treatment effects in patients who did or did not recently take an ACE-inhibitor/ARB for all key outcomes; with statistically significant differences between sacubitril/valsartan and ACE-inhibitor/ARB treatment groups for hospitalisations, and the composite outcome of all-cause mortality and hospitalisations.

6.23 The ESC considered while it was reasonable to conclude that sacubitril/valsartan would likely be effective for ACE inhibitor/ARB-naïve HF patients, it was difficult to draw comparative conclusions due to the quality of available evidence.

6.24 The Pre-PBAC Response argued that many patients who are currently treated with ACE inhibitors or ARBs are not adequately managed on current treatment, and the evidence presented in the PARADIGM-HF trial demonstrated the superiority of sacubitril/valsartan over ACE inhibitors (enalapril) in patients with reduced ejection fraction. The Pre-PBAC Response further argued therefore that as superiority has been adequately demonstrated, it must follow that patients who remain on ACE inhibitors or ARBs are receiving sub-optimal treatment and noted the letter of support from clinicians noted it, 'goes against clinical judgement to wait for the patient to be hospitalised before commencing sacubitril/valsartan'. The PBAC disagreed and

considered the evidence presented did not support the claim that all patients on ACE inhibitors are inadequately treated.

Analyses to inform LVEF 41%-49% population

6.25 Results of the pooled analysis of sacubitril/valsartan versus enalapril or valsartan (Solomon 2020), grouped by ejection fraction categories, are presented in the table below.

Table 8: Treatment effect (sacubitril/valsartan vs enalapril or valsartan) for LVEF categories ≤ 40%, >40% to 50% and >50%, Solomon 2020

Outcome	*LVEF ≤ 40% n=8397*	*LVEF >40% to 50% [a] n=730*	*LVEF > 50% n=4067*
First HF hospitalisation or CV death			
Events, n	*2031*	*214*	*869*
Hazard Ratio (95% CI)	***0.80 (0.73, 0.87)***	*0.85 (0.65, 1.12)*	*0.94 (0.82, 1.08)*
First HF hospitalisation			
Events, n	*1195*	*146*	*692*
Hazard Ratio (95% CI)	***0.79 (0.71, 0.89)***	*0.81 (0.59, 1.13)*	*0.93 (0.80, 1.08)*
CV death			
Events, n	*1251*	*100*	*316*
Hazard Ratio (95% CI)	***0.80 (0.71, 0.89)***	*0.98 (0.66, 1.46)*	*0.96 (0.77, 1.20)*
Total HF hospitalisation and CV death			
Events, n	*3179*	*354*	*1549*
Hazard Ratio (95% CI)	***0.79 (0.71, 0.87)***	*0.80 (0.59, 1.08)*	*0.90 (0.76, 1.06)*
Total HF hospitalisation			
Events, n	*1928*	*254*	*1233*
Hazard Ratio (95% CI)	***0.78 (0.68, 0.90)***	*0.73 (0.50, 1.07)*	*0.88 (0.73, 1.06)*

Source: Supplemental Table 1, Solomon 2020

Abbreviations: CV, cardiovascular; HF, heart failure; LVEF, left ventricular ejection fraction

[a] The PARADIGM-HF trial included patients with LVEF ≤40%, and the PARAGON-HF trial included patients with LVEF ≥45%, meaning no patients with LVEF measured between 41% and 44% were included in this pooled analysis. However, the study authors argued that because of the imprecise nature of LVEF measurement, participants were likely enrolled outside these bounds such that this mid-range of LVEF would have been well represented in the pooled analysis. The study authors also stated that many LVEF assessments in their analysis were rounded to the nearest 5%, which suggests semi-quantitative estimation by site investigators and reflects real-world clinical practice.

6.26 There were no statistically significant differences between treatments for patients with LVEF >40% to 50% for any of the reported clinical outcomes. However, point estimates were similar to those with ejection fraction ≤40%, with smaller patient numbers in this group potentially influencing the outcome of the statistical analysis. The study authors suggested that patients with ejection fraction lower than normal, which includes patients with "mid-range" ejection fraction or borderline ejection fraction, would likely benefit from sacubitril/valsartan compared with an ACE-inhibitor or ARB.

6.27 Due the limited available evidence, the ESC considered the comparative effectiveness of sacubitril/valsartan in the LVEF 40%-49% population compared to both an LVEF <40% population and enalapril in the LVEF 40%-49% population was uncertain.

6.28 The Pre-PBAC Response argued the requested change to the LVEF threshold was consistent with CSANZ guidelines and that the margin of error in echocardiogram measurement meant some patients with a true LVEF of ≤40%, who should be eligible

for treatment with sacubitril/valsartan, would be ineligible for treatment. The PBAC considered that, while there may be a margin of error with respect to measurement of ejection fraction, the argument was insufficient to justify such a change to the listing of sacubitril/valsartan. The PBAC also noted that this same margin of error would have been present in assessing eligibility for inclusion in the PARADIGM-HF Trial and therefore the argument is not relevant. The PBAC reiterated that such a request must be supported by adequate clinical data and economic analysis to demonstrate effectiveness and cost effectiveness in the requested population.

Analyses to inform beta-blocker population

6.29 The CIBIS III study found no differences in terms of efficacy and safety between patients who initiated treatment with an ACE-inhibitor first, or those who initiated treatment with a beta-blocker first, including the primary endpoint of time to first event of all-cause mortality or all-cause hospitalisation (178 patients (35.2%) bisoprolol-first; 186 (36.8%) enalapril-first; HR 0.94, 95% CI 0.77, 1.16). In the bisoprolol-first group, last prescribed doses of bisoprolol were significantly higher as compared with the enalapril-first group ($p<0.001$). In the enalapril-first group, last prescribed doses of enalapril were significantly higher as compared with the bisoprolol-first group ($p<0.001$). These results suggest that the first-initiated therapy is more likely to be up-titrated to the target dose. It is unclear whether the results of this study would be equally applicable to the treatment order of sacubitril/valsartan and a beta-blocker, but results suggest that patients initiated on sacubitril/valsartan prior to a beta-blocker could be less likely to receive the maximum tolerated dose of a beta-blocker than patients who receive treatment in the order currently specified in the PBS restriction.

Comparative harms

6.30 Key adverse events in the PIONEER-HF and TRANSITION trials are presented in the table below.

Table 9: Summary of key adverse events in the randomised trials

Trial ID	PIONEER-HF			TRANSITION Sacubitril/valsartan		
	Sacubitril/ valsartan N=440 n (%)	Enalapril N=441 n (%)	RR (95% CI), unless indicated	Pre-discharge (N=495)	Post-discharge (N=496)	RR (95% CI)
Deaths	10 (2.3)	15 (3.4)	HR 0.66 (0.30, 1.48)	13 (2.6)	10 (2.0)	1.30 (0.58, 2.94)
Adverse events, patients	NR	NR	NR	342 (69.1)	325 (65.5)	1.05 (0.97, 1.15)
SAE, patients	NR	NR	NR	93 (18.8)	89 (17.9)	1.05 (0.81, 1.36)
Discontinuation due to AE	51 (11.5)	45 (10.1)	NR	35 (7.1)	28 (5.6)	1.25 (0.77, 2.03)
Discontinuation due to SAE	NR	NR	NR	17 (3.4)	14 (2.8)	1.22 (0.61, 2.44)
Treatment-emergent adverse events (>5% of patients in either treatment group):						
Acute kidney injury	36 (8.2)	37 (8.5)	NR	NR	NR	NR
Blood creatinine increased	31 (7.1)	19 (4.4)	NR	17 (3.4)	12 (2.4)	1.42 (0.69, 2.94)
Renal impairment	NR	NR	NR	25 (5.1)	16 (3.2)	1.57 (0.85, 2.90)
Cardiac failure congestive	22 (5.0)	32 (7.3)	NR	35 (7.1)	42 (8.5)	0.84 (0.54, 1.28)
Dizziness	39 (8.9)	33 (7.6)	NR	28 (5.7)	21 (4.2)	1.34 (0.77, 2.32)
Hyperkalaemia	55 (12.5)	40 (9.2)	NR	56 (11.3)	56 (11.3)	1.00 (0.71, 1.42)
Hypotension	79 (18.0)	79 (18.1)	NR	63 (12.7)	47 (9.5)	1.34 (0.94, 1.92)
Key safety outcomes, PIONEER-HF trial:						
Worsening renal function [a]	60 (13.6)	65 (14.7)	0.93 (0.67, 1.28)	NA		
Hyperkalaemia [b]	51 (11.6)	41 (9.3)	1.25 (0.84, 1.84)			
Symptomatic hypotension	66 (15.0)	56 (12.7)	1.18 (0.85, 1.64)			
Angioedema	1 (0.2)	6 (1.4)	0.17 (0.02, 1.38)			

Source: Figure 2.6, p38 of the submission; Table S3, Velazquez 2019 publication, supplementary appendix; TRANSITION publication supplementary appendix.

Abbreviations: AE, adverse event; CI, confidence interval; HR, hazard ratio; n, number of participants reporting data; N, total participants in group; NR, not reported; RR, relative risk; SAE, serious adverse event

[a] Worsening renal function was defined as an increase in serum creatinine concentration ≥ 0.5 mg/dL, and decrease in eGFR ≥25%.

[b] For the safety outcome, hyperkalaemia was defined as K+ >5.5 mEq/L

6.31 There were no significant differences between treatment groups for occurrence of key safety outcomes including renal insufficiency, hyperkalaemia, symptomatic hypotension or angioedema. Approximately 10% of patients in each treatment arm of PIONEER-HF discontinued treatment due to an adverse event. In the TRANSITION trial, fewer patients discontinued treatment due to adverse events (7.1% in pre-discharge group, 5.6% in post-discharge group), and adverse event rates were relatively consistent between treatment groups. In both trials the most commonly reported adverse events were hyperkalaemia and hypotension.

6.32 The results of the retrospective cohort study (Tan 2020) found there was a statistically significantly higher rate of hypotension in the sacubitril/valsartan-treated cohort compared to those treated with an ACE-inhibitor/ARB. The submission stated that this was consistent with the safety profile from the key sacubitril/valsartan clinical trial (PARADIGM-HF).

Subgroup analyses to inform safety in ACE-inhibitor/ARB-naïve population

6.33 Key safety outcomes from PIONEER-HF by prior experience with ACE-inhibitors/ARBs are presented in the table below.

Table 10: Pre-specified subgroup analysis of safety outcomes – PIONEER-HF

Outcome (n, %)	ACE-inhibitor/ARB-naive			ACE-inhibitor/ARB experienced		
	Sacubitril/ valsartan N=232	Enalapril N=227	RR (95% CI)	Sacubitril/ valsartan N=208	Enalapril N=214	RR (95% CI)
Worsening renal function [a]	35 (15.1)	32 (14.1)	1.07 (0.69, 1.67)	40 (19.2)	43 (20.1)	0.96 (0.65, 1.41)
Hyperkalaemia [b]	29 (12.5)	22 (9.7)	1.29 (0.76, 2.18)	22 (10.6)	19 (8.9)	1.19 (0.66, 2.13)
Symptomatic hypotension	38 (16.4)	29 (12.8)	1.28 (0.82, 2.01)	28 (12.5)	27 (12.6)	1.07 (0.65, 1.75)
Angioedema [c]	1 (0.4)	2 (0.9)	0.49 (0.04, 5.36)	0 (0)	4 (1.9)	NA

Source: Figure 2.8, p39 of the submission.

Abbreviations: ACE, angiotensin converting enzyme; ARB, angiotensin II receptor blocker; CI, confidence interval; NA, not applicable; RR, relative risk

[a] Worsening renal function was defined as an increase in serum creatinine concentration ≥ 0.5 mg/dL, and decrease in eGFR ≥25%.

[b] For the safety outcome, hyperkalaemia was defined as K+ >5.5 mEq/L

[c] Positively-adjudicated angioedema cases only.

6.34 There were no significant differences between sacubitril/valsartan and enalapril treatment groups for patients with or without prior use of ACE-inhibitors/ARBs.

Analyses to inform safety in LVEF 41%-49% population

6.35 The Solomon (2020) publication reported that there was no interaction between treatment and LVEF for any of the measured safety endpoints. The study noted greater rates of hypotension and hyperkalaemia in patients with lower ejection fraction.

Analyses to inform safety in beta-blocker population

6.36 The CIBIS III publication (Willenheimer 2005) reported that there were no differences in the proportions of patients experiencing adverse events or serious adverse events in the bisoprolol-first group or the enalapril-first group.

Clinical claim

6.37 The submission described sacubitril/valsartan as superior in terms of effectiveness compared to ACE-inhibitors (enalapril). ESC agreed with the evaluator that the therapeutic conclusion of superior efficacy was inadequately supported by the evidence presented in the submission, given the issues described above with regards to the applicability of PIONEER-HF population and subgroup analyses.

6.38 The submission further argued that patients in the PIONEER-HF trial would achieve a similar magnitude of benefit from treatment with sacubitril/valsartan as observed in the PARADIGM-HF trial, which was the primary evidence considered by the PBAC in the previous submissions for sacubitril/valsartan (March, July and August 2016). The PBAC previously considered that the clinical claim of superior comparative effectiveness compared to enalapril was reasonable, but noted that it was difficult to quantify the magnitude of this benefit accurately (Section 6.25, sacubitril/valsartan, PBAC Public Summary Document (PSD), March 2016). However, results from the PIONEER-HF trial and the PARADIGM-HF trial were derived from different patient populations and at different time points, limiting the comparability of these results.

6.39 The submission described sacubitril/valsartan as similar in terms of safety compared to enalapril, with no significant differences in safety between ACE-inhibitor/ARB-naïve versus -experienced subgroups. This claim may be reasonable.

6.40 The ESC noted there were substantial gaps and limitations with the presented data and analyses. The ESC therefore considered the clinical claim was difficult to assess within the context of the submission brought forth by the sponsor.

6.41 Regarding the clinical claims in the submission, the PBAC considered:

- The claim of superior comparative effectiveness to enalapril (as a proxy for all ACE inhibitors) for the requested populations was inadequately supported due to applicability issues with the PIONEER-HF population and reliability of the subgroup analysis.
- The claim that patients would receive a similar magnitude of benefit in the expanded populations, compared to the currently subsidised sacubitril/valsartan population, was uncertain as the results of the PIONEER-HF and PARADIGM-HF trials were in different populations and of uncertain comparability.
- The claim of non-inferior/similar comparative safety to enalapril was reasonable.

Economic analysis

6.42 The submission did not present an economic evaluation, arguing that the magnitude of benefit is the same in patients with versus without prior exposure to an ACE-inhibitor or ARB, and there are no proposed changes to the price for sacubitril/valsartan. The current prices (published and effective, including Special Pricing Arrangement) for sacubitril/valsartan are to be applied to patients in the ACE-inhibitor/ARB-naïve population. This was inappropriate. The cost effectiveness of sacubitril/valsartan in the expanded patient population has not been established.

6.43 The PSCR argued the results of the PIONEER-HF trial demonstrated the magnitude of benefit in the current and requested sacubitril/valsartan PBS populations was the same, irrespective of prior ACE inhibitor/ARB therapy and that the magnitude of benefit for the whole trial population was consistent with that observed in the PARADIGM-HF trial. The ESC disagreed with the PSCR and considered the available information was uninformative for decision making. The ESC further considered that an assumption of cost effectiveness cannot be reasonably conferred because:

- For the requested expanded population with LVEF 40%-49%, the ESC considered this population would have a lower risk of mortality or hospitalisation due to heart failure and therefore the magnitude of benefit with sacubitril/valsartan treatment would likely be lower; and

- Due to the magnitude of price difference between sacubitril/valsartan and PBS listed ACE inhibitors and ARBs, first line use of sacubitril/valsartan would not be as cost effective as the current PBS listing for the cohort of patients who would otherwise be adequately controlled with these less costly alternatives.

6.44 The ESC considered that, as an assumption of equivalent cost effectiveness between the current population and the requested listing was inappropriate and inadequately justified, a full cost effectiveness analysis would be required to evaluate the requested change to listing. The ESC also considered that listing on a cost minimisation basis with ACE inhibitors/ARBs for the expanded population may be reasonable in the absence of a modelled cost effectiveness analysis.

Drug cost/patient/year

Table 11: Drug cost per patient for proposed and comparator drugs

	Sacubitril/valsartan Trial dose and duration	Sacubitril/valsartan Financial estimates	Enalapril Trial dose and duration	ACE-inhibitors/ARBs Financial estimates
Mean dose	Dose dependent on SBP, 24/26 mg to 97/103 mg twice daily	49/51 mg twice daily	Dose dependent on SBP, 5 mg/day to 20mg/day	N/A [a]
Mean duration	8 weeks	ongoing	8 weeks	ongoing
Cost/patient/month (effective price for sacubitril/valsartan)	Flat pricing across all dose strengths $[redacted]	Flat pricing across all dose strengths $[redacted]	Average DPMQ for all dose strengths $14.44	ACE-inhibitor: $14.93 ARBs: $14.44
Cost/patient/year (13.04 scripts/patient/year)	$[redacted]	$[redacted]	$188.30	ACE-inhibitor: $194.69 ARBs: $188.30

Source: Compiled during the evaluation

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; SBP, systolic blood pressure

[a] In the financial estimates, the comparator was all dose strengths of all PBS-listed ACE-inhibitors and ARBs, with an average price utilised for calculation of cost-offsets. Cost/patient/month and /year are approximate, as these comparators vary in cost and whether there are 28 or 30 days of treatment per script.

Estimated PBS usage & financial implications

6.45 This submission was considered by DUSC. The submission stated that an epidemiological approach was taken in estimating utilisation in the new patient population. The submission attempted to estimate utilisation in the new patient population based on a proportion of the growth rates in existing prescriptions. This was inappropriate, and estimates of utilisation drawn from this approach do not appear to meet face validity.

Table 12: Key inputs for financial estimates

Parameter	Value applied and source	Comment
Currently eligible population (scripts)	Current PBS script data for sacubitril/valsartan, extrapolated using average monthly growth in script numbers (1036 scripts /month) from June 2019 to April 2020. Year 1 – [redacted][1] scripts, increasing to Year 6 – [redacted][2] scripts.	Unclear if underestimate or overestimate. Monthly average growth varies widely depending on 12 month period used. Does not take into account potential for increased use in currently eligible patients with expansion of restriction.
Additional growth: patients with LVEF% ≤40%, and 41-49% (number of scripts)	Distribution of LVEF% across the chronic heart failure population from the SHAPE study (Sindone 2019), adjusted to exclude patients with LVEF >50%. Calculated based on current PBS script data ≤40%: 72.6% (accounted for in currently eligible pop'n) 40-49%: 27.4% (growth < 500 scripts/month)	Highly uncertain estimates with proportional growth estimated from current script numbers and not the total pool of potentially eligible patients. Retrospective cohort study in Australian primary care setting. Only a small proportion of study participants (4.5%) had LVEF results available (982/21,878 patients with definite/probable heart failure). Limited data available from publication – conference abstract.
Additional growth: patients not currently treated with ACE-inhibitor or ARB (34%)	Complement of proportion of patients with de novo HF and LVEF≤40% prescribed ACE-inhibitor/ARB at discharge from hospitalisation for acute heart failure from the SNAPSHOT-HF Study (Newton 2016), a prospective audit of consecutive patients to hospitals in NSW and ACT. Calculated based on proportions of current PBS script data Prescribed ACE-inhibitor/ARB: 66% (accounted for in currently eligible pop'n) Not prescribed ACE-inhibitor/ARB: 34% (500 to < 5,000 scripts/month)	Highly uncertain estimates with proportional growth estimated from current script numbers and not the total pool of potentially eligible patients. Rates of ACE-inhibitor/ARB use may be lower in some patients, therefore increasing the proportion of ACE-inhibitor/ARB-naïve patients. Unclear whether these proportions of use would be applicable to non-hospitalised patients. No accounting for potential overlap between subgroups.
Uptake rates	Differ by sub-group: EF% 41-49%: 66% in Yr 1 increasing to 80% in Yr 6 ACE-inhibitor/ARB-naïve: 30% in Yr 1 increasing to 66% in Yr 6. Based on assumptions around ease of clinician identification of eligible patients.	Assumptions, highly uncertain. Other factors affecting uptake have not been considered. Script numbers for currently eligible patients already implicitly capture uptake rates, meaning that application of an uptake rate for subgroups may underestimate utilisation.
Offsets for comparator	All sacubitril/valsartan scripts were assumed to substitute for one script of an ACE-inhibitor/ARB	Does not take into account patients intolerant to treatment with ACE-inhibitor/ARB.

Source: Section 4 - Utilisation-and-cost-model_Entresto_July2020.xlsx.

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; EF, ejection fraction; HF, heart failure

The redacted values correspond to the following ranges:

[1] 400,000 to < 500,000

[2] *1,000,000 to < 2,000,000***Table 13: Estimated use and financial impact with expanded PBS restriction (newly eligible patients only)**

	Year 1 2020-21 [a]	Year 2 2021-22	Year 3 2022-23	Year 4 2023-24	Year 5 2024-25	Year 6 2025-26
Currently eligible patients						
Scripts (all dose strengths [b])	[redacted][1]	[redacted][2]	[redacted][3]	[redacted][4]	[redacted][5]	[redacted][5]
Patients (total uptake) [c]	[redacted][6]	[redacted][7]	[redacted][8]	[redacted][9]	[redacted][10]	[redacted][10]
Newly eligible patients						
Scripts - LVEF 40-49% [d]	[redacted][11]	[redacted][11]	[redacted][11]	[redacted][11]	[redacted][11]	[redacted][11]
Scripts - ACE/ARB-naïve [e]	[redacted][11]	[redacted][11]	[redacted][11]	[redacted][11]	[redacted][11]	[redacted][11]
Total additional scripts	[redacted][12]	[redacted][12]	[redacted][12]	[redacted][12]	[redacted][12]	[redacted][12]
Total additional patients	[redacted][11]	[redacted][11]	[redacted][11]	[redacted][11]	[redacted][11]	[redacted][11]
Total cost sacubitril/valsartan – newly eligible patients only						
Total cost (effective)	[redacted][13]	[redacted][13]	[redacted][13]	[redacted][13]	[redacted][14]	[redacted][14]
Less co-payments	[redacted][13]	[redacted][13]	[redacted][13]	[redacted][13]	[redacted][13]	[redacted][13]
Net cost (effective)	[redacted][13]	[redacted][13]	[redacted][13]	[redacted][13]	[redacted][13]	[redacted][13]
Estimated change in ACE-inhibitor/ARB prescriptions – newly eligible patients only						
ACE-inhibitor scripts (46%)	[redacted][11]	[redacted][11]	[redacted][11]	[redacted][11]	[redacted][11]	[redacted][11]
ARB scripts (54%)	[redacted][11]	[redacted][11]	[redacted][11]	[redacted][11]	[redacted][11]	[redacted][11]
Total	[redacted][12]	[redacted][12]	[redacted][12]	[redacted][12]	[redacted][12]	[redacted][12]
Cost-offsets for ACE-inhibitor/ARB scripts – newly eligible patients only						
Cost offsets to PBS/RPBS	[redacted][13]	[redacted][13]	[redacted][13]	[redacted][13]	[redacted][13]	[redacted][13]
Less co-payments	[redacted][13]	[redacted][13]	[redacted][13]	[redacted][13]	[redacted][13]	[redacted][13]
Net offsets to PBS/RPBS	[redacted][13]	[redacted][13]	[redacted][13]	[redacted][13]	[redacted][13]	[redacted][13]
Net financial implications						
Cost PBS/RPBS (effective)	[redacted][13]	[redacted][13]	[redacted][13]	[redacted][13]	[redacted][13]	[redacted][13]
Net cost PBS/RPBS (effective), excluding co-payment	[redacted][13]	[redacted][13]	[redacted][13]	[redacted][13]	[redacted][13]	[redacted][13]

Source: Table 4.3, p55; Table 4.8, p58; Table 4.12 and 4.13, p60; Table 4.16, p62; Table 4.17, p63; of the submission; Section 4 - Utilisation-and-cost-model_Entresto_July2020.xlsx.

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; LVEF, left ventricular ejection fraction.

[a] The submission presented utilisation and cost data for 12 month periods from June to May for each year of listing.

[b] Increase of 500 to < 5000 patients/month, extrapolated linearly across years of listing. Distribution by dose strengths at January 2020 (24/26 mg, 37%; 49/51 mg, 33%; 97/103 mg, 30%) applied across all years of listing, to both current and newly eligible scripts.

[c] The submission back-calculated estimated patient numbers by dividing total script numbers by 13.04 scripts/patient/year, then applying an assumed adherence rate of 75% based on ACE-inhibitor/ARB adherence in patients with ischaemic heart disease (Roughead 2010).

[d] Incremental increase of < 500 scripts/month for all eligible patients, with estimated uptake rates of 66% in Year 1, increasing to 80% in Year 6 of listing. Discontinuations were not accounted for.

[e] Incremental increase of 500 to < 5000 scripts/month for all eligible patients, with estimated uptake rates of 30% in Year 1, increasing to 66% in Year 6 of listing. Discontinuations were not accounted for.

Note: Estimated costs for the newly eligible patient population were calculated during the evaluation. The submission presented overall costs for both the currently eligible and newly eligible population.

The redacted values correspond to the following ranges:

[1] 400,000 to < 500,000
[2] 600,000 to < 700,000
[3] 700,000 to < 800,000
[4] 900,000 to < 1,000,000
[5] 1,000,000 to < 2,000,000
[6] 40,000 to < 50,000
[7] 60,000 to < 70,000
[8] 70,000 to < 80,000
[9] 90,000 to < 100,000
[10] 100,000 to < 200,000
[11] 500 to < 5,000
[12] 5,000 to < 10,000
[13] $0 to < $10 million
[14] $10 to < $20 million

6.46 The estimated total net cost to the PBS/RPBS for the newly eligible patients for sacubitril/valsartan (excluding patient co-payments) was $0 to < $10 million in Year 1 of listing, increasing to $0 to < $10 million in Year 6, a cumulative total of $0 to < $10 million in the first 6 years of listing.

6.47 The estimated total net cost to the PBS/RPBS of the expanded listing (both current and newly eligible patients) for sacubitril/valsartan (excluding patient co-payments) was $50 to < $60 million in Year 1 of listing, increasing to $100 to < $200 million in Year 6, a total net cost of $500 to < $600 million in the first 6 years of listing.

6.48 The submission's estimates of utilisation and financial impact were highly uncertain. Using the numbers of current and new scripts estimated across the 6 years of listing in the submission, the new patients represent an incremental increase of only 0.7% of the existing patient population. The validity of attempting to estimate utilisation in the new population based on a proportion of growth rates in existing prescription numbers is highly uncertain. The number of prescriptions currently issued for sacubitril/valsartan does not represent the entirety of the eligible chronic heart failure population in Australia. This approach also does not take into account patients who have been prescribed an ACE-inhibitor/ARB but are not yet stabilised on this treatment – these patients would be eligible for treatment under the new restriction but not the existing restriction, but would not be considered to be ACE-inhibitor/ARB-naïve. Furthermore, the submission applied an uptake rate to prescriptions for newly eligible patients (with the rates themselves uncertain and poorly supported in the submission). However, current script numbers already implicitly capture an uptake rate (as not all currently eligible patients are likely to be treated with sacubitril/valsartan). Given the proposed changes to the PBS restriction moves sacubitril/valsartan to an earlier line of therapy, the number of new prescriptions for the expanded restriction may be considerably underestimated.

6.49 A summary of the Drug Utilisation Sub-Committee advice to the PBAC is presented below.

DUSC considers the estimates presented in the submission to be highly uncertain. The main issues are:

- *In some patients there is an overlapping pathophysiology of heart failure with reduced ejection fraction and heart failure with preserved ejection fraction. With the recognition of a mid-range ejection fraction population and the increase in the arbitrary measure of left ventricular ejection fraction (LVEF), this would likely cause an influx of patients who would not receive benefit from sacubitril/valsartan.*
- *There is evidence that treatment sequences do affect which medications are up-titrated to their maximal dosing. It is suggested that the priority of up-titrating the beta blocker to the targeted dose unless contraindicated should be explicitly mentioned in the restriction.*
- *The cost effectiveness of sacubitril/valsartan as first line therapy has not been established and a large proportion of patients may be adequately treated with an angiotensin-converting enzyme inhibitor (ACE-I)/angiotensin receptor blocker (ARB). The concern from clinicians presented in the Pre-Sub-Committee Response (PSCR) is noted however analyses have not been provided to support the requested changes.*
- Whether the estimated utilisation in the new patient population is plausible given substantial uncertainties with the measure of growth in the existing PBS population, the method of estimating use in new patients from existing sacubitril/valsartan uptake based on a proportion of growth rates in existing prescriptions, data sources used to estimate the size of the new PBS population, and rates of uptake in the new population.
- *Whether the patient estimates are reliable as they are based on a back calculation of variable monthly average utilisation data for sacubitril/valsartan. This was also impacted by the additional variation in utilisation in response to COVID-19.*
- *There is likely an overlap between the naïve to ACE-I/ARB population and the population of patients with an LVEF 41-49%. The SNAPSHOT-HF study used to establish patients who were naïve to ACE-I/ARB therapy looked at patients being discharged from hospital after being diagnosed with acute heart failure. This may not be representative of the broader population as the non-hospitalised setting typically has a larger proportion of 'low-risk' heart failure patients[1] and hence may underestimate the naïve population.*
- *The uptake rates were not justified and likely underestimated due to the familiarity of clinicians with sacubitril/valsartan.*
- *The adherence to medications in the new population is likely overestimated due to their potentially less severe diagnosis.*

QUM

- The sponsor did not present any quality use of medicines information. In the previous consideration of sacubitril/valsartan there were a number of quality use of medicines issues that were raised and may impact negatively on the safety of this

medication. These issues are as follows (Section 6.50, sacubitril valsartan PSD – March 2016 PBAC Meeting):
    - risk of accidental co-prescribing with ARBs or ACE inhibitors.
    - risk of confusion about valsartan doses due to the increase in bioavailability when it is combined with sacubitril.
    - risk of adverse drug reactions from statins as co-prescribing sacubitril with statins, which is likely to occur in most patients, increases exposure to statins.
- *DUSC noted that the letter from the cardiologists presented by the sponsor represents a quality use of medicines issue where patients may receive a less cost effective treatment displacing ACE-I/ARB + beta blocker which may adequately manage their condition but take longer to up-titrate.*

6.50 The Pre-PBAC Response argued that any increase in use of sacubitril/valsartan in the expanded population would be substantially below the current caps in the current risk sharing arrangement. The PBAC did not accept this argument and considered the inherent uncertainties in the utilisation and financial estimates meant such a conclusion was highly speculative.

Quality Use of Medicines

6.51 The submission did not present any quality use of medicines information. In the previous consideration of sacubitril/valsartan there were a number of quality use of medicines issues raised: risk of accidental co-prescribing with ARBs or ACE inhibitors; risk of confusion about valsartan doses due to the increase in bioavailability when combined with sacubitril; risk of adverse drug reactions from co-prescribing sacubitril with statins (increases exposure to statins) (Section 6.50, sacubitril/valsartan, PBAC PSD, March 2016). All these quality use of medicines issues will apply equally to the expanded patient population requested in this submission.

Financial Management – Risk Sharing Arrangements

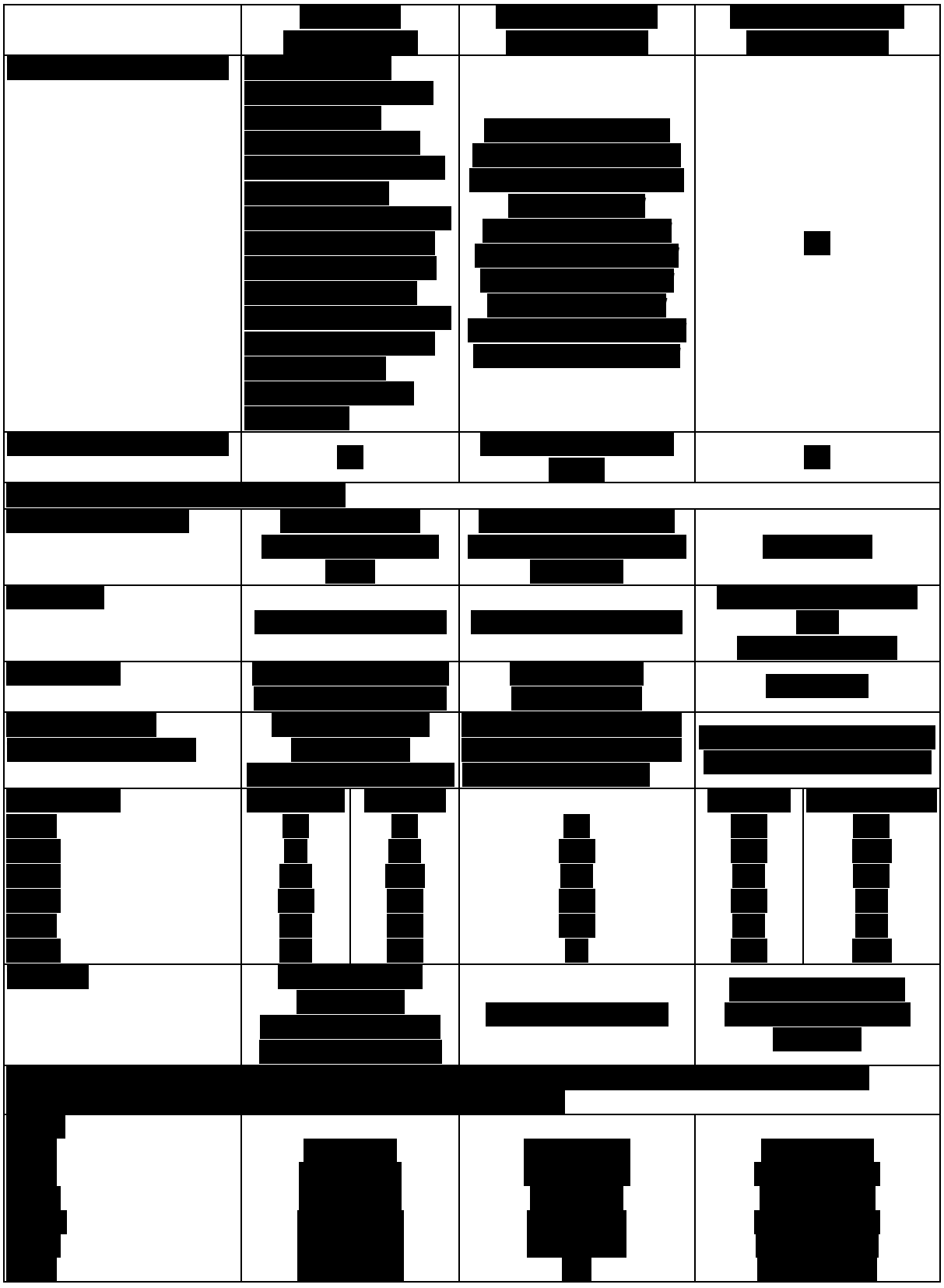
6.52 Sacubitril/valsartan currently has a risk share arrangement, and the sponsor stated that any additional use should also be subject to this arrangement. Sacubitril/valsartan is listed with a Special Pricing Arrangement and subsidisation caps. The submission argued that the expected increase in utilisation of sacubitril/valsartan relating to the proposed expanded PBS listing is substantially less than the capping levels previously set for Years 4 and 5 (of the previous listing, corresponding to Years 1 and 2 of the current requested listing). The sponsor argued that utilisation was likely to remain lower than any future capping levels.

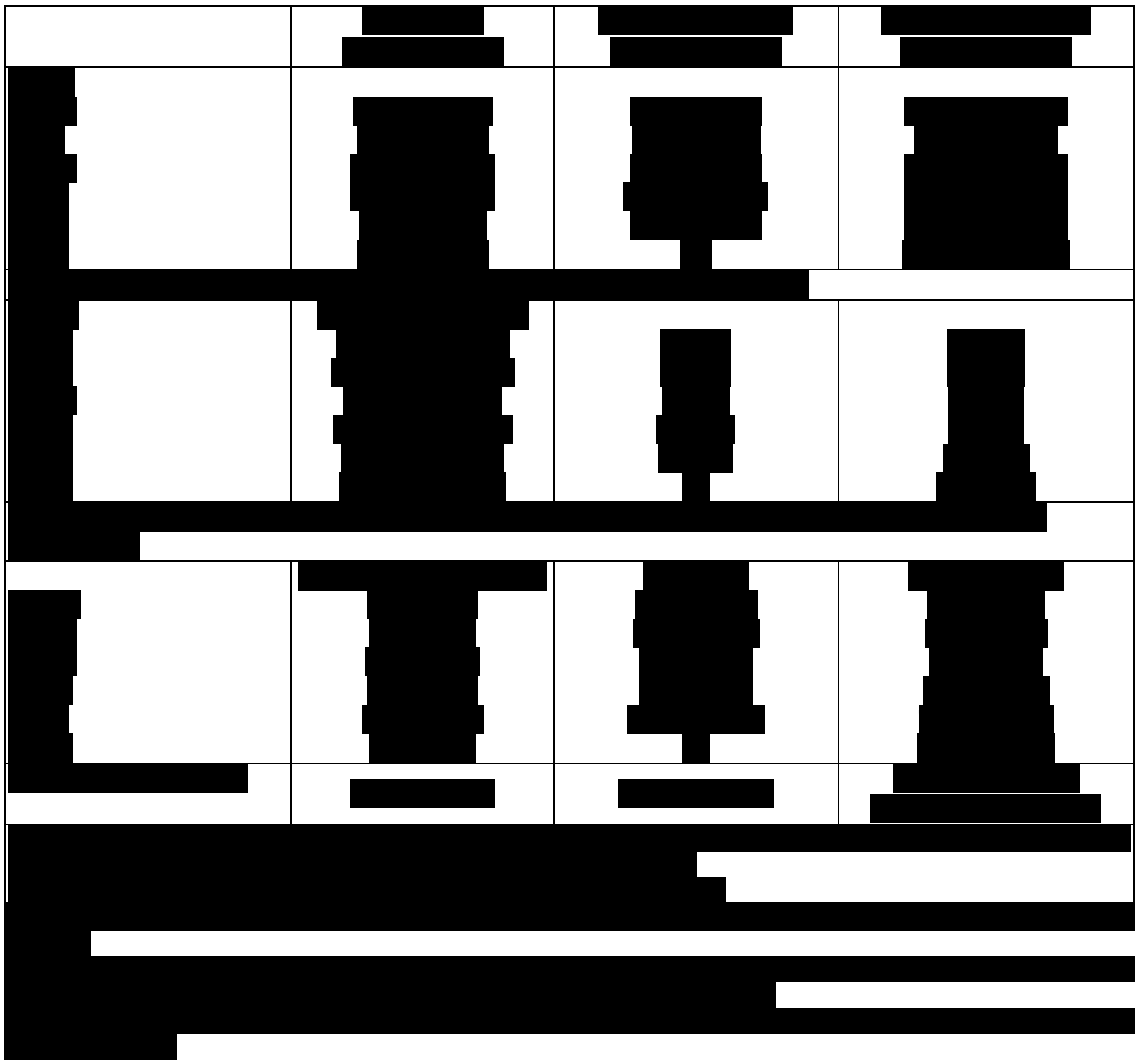
For more detail on PBAC's view, see section 7 PBAC outcome.

[1] Ferreira J, et al. Heart failure in the outpatient versus inpatient setting: findings from the BIOSTAT-CHF study. European Journal of Heart Failure. 2019;21(1):112-120

Committee-In-Confidence information

[redacted]





End Committee-In-Confidence information

7 PBAC Outcome

7.1 The PBAC noted the submission lacked standard information expected in a major submission, including the literature search, clinical trial reports, economic analysis, clinical study reports (CSRs) and discussion of the applicability of trial data to PBS population. These deficiencies impeded the Committee's ability to consider the submission. The Committee agreed any resubmission should include all standard information expected in a major submission.

7.2 With respect to the core propositions of the submission, the PBAC did not recommend amending the listing of sacubitril/valsartan to amend the ejection fraction threshold in the restriction to include patients with an LVEF between 41% - ≤50% (from the current ≤40%), nor to remove the requirements for prior treatment with an ACE

inhibitor or ARB before commencing treatment. However, with respect to the requirement for patients to be on a maximally tolerated dose of a beta-blocker prior to commencing treatment, the PBAC recommended amending the listing, noting the current wording was inconsistent with clinical guidelines and may complicate clinical management of patients. The PBAC also recommended changes to nurse practitioner prescribing arrangements. These four outcomes are discussed individually below.

7.3 The PBAC considered the nominated comparator of enalapril, as a proxy for all ACE inhibitors and previously accepted by the PBAC for the current sacubitril/valsartan population, was reasonable.

7.4 The PBAC considered the request to amend the listing to permit use in patients with an LVEF of ≤50% was poorly justified, as no data or economic analysis was presented to support the position that sacubitril/valsartan was of equivalent cost effectiveness to its current listing in this expanded population. The Committee noted the Solomon 2020 pooled analysis of the PARADIGM-HF and PARAGON-HF trials indicated similar point estimates for the sacubitril/valsartan versus enalapril or valsartan comparisons in both the LVEF ≤40% and >40% - ≤50% populations in terms of heart failure related hospitalisations or cardiovascular death. However, the PBAC considered the subgroup analyses in Solomon 2020 were uncertain, as clinical measures were secondary outcomes in one of the included studies and sample sizes differed between the LVEF groups. Furthermore, the PBAC noted the LVEF >40% - ≤50% population had less severe disease than the currently eligible population, and were likely to have better prognoses; an assumption of equivalent cost effectiveness to a population with more severe disease was considered highly implausible. Therefore, the PBAC did not accept the claim that a cost minimisation to the current sacubitril/valsartan LVEF ≤40% population was appropriate. While the Committee noted the argument in the Pre-PBAC Response that there was a margin of error in echocardiogram measurements of LVEF that meant some patients with a true LVEF ≤40% may not be treated, the Committee felt that this also applied to the PARADIGM-HF study and hence was not applicable and was certainly insufficient to justify the requested change in the absence of a modelled cost effectiveness analysis to support the use of sacubitril/valsartan in this population.

7.5 The PBAC noted the request to remove the requirement for prior treatment with an ACE inhibitor or ARB would have the net effect of placing sacubitril/valsartan as a first line treatment option for the LVEF ≤40% population. The Committee considered that whilst the presented evidence in the PARADIGM HF and PIONEER HF trials supported a conclusion that sacubitril/valsartan was of similar effectiveness and safety in the ACE inhibitor/ARB-naïve and experienced populations, the cost effectiveness of sacubitril/valsartan would be different when used in a first or second line setting. Given the magnitude of price difference between sacubitril/valsartan and first-line ACE inhibitors and ARBs, the PBAC considered sacubitril/valsartan would likely not be cost effective at current price when replacing these agents in a first line setting, as some patients would otherwise be adequately treated on these substantially less

costly therapies and sacubitril/valsartan would not provide better outcomes in these patients. Therefore, the PBAC considered a modelled cost effectiveness analysis would be required to establish the cost effectiveness of sacubitril/valsartan as a first line therapy, which would likely indicate the need for a substantial price reduction for use in this setting to be cost effective. Alternatively, the PBAC considered a cost minimisation analysis with ACE inhibitors and ARBs for use in this setting may be reasonable in the absence of a formal cost effectiveness analysis.

7.6 The PBAC noted the current beta-blocker requirement in the sacubitril/valsartan restriction requires a patient to be at the maximally tolerated dose (unless contraindicated or not tolerated). The PBAC considered this requirement inconsistent with clinical guidelines and may complicate management of patients. The Committee noted the CSANZ Guidelines do not recommend patients with congested disease commence heart failure treatment with beta-blockers and provide flexibility for whether patients with euvolaemic disease should commence treatment with a beta-blocker. The Committee agreed it would be appropriate for the listing of sacubitril/valsartan to be more flexible in regard to the timing and dosing of beta-blocker therapy. As such, the PBAC recommended the phrase 'must include the maximum tolerated dose of a beta-blocker, unless contraindicated or not tolerated' should be amended to, 'which should include a beta-blocker, unless contraindicated or not tolerated' to allow for individual prescriber decision making.

7.7 The PBAC considered it was reasonable to clarify that nurse practitioner prescribing arrangements for continuing therapy includes prescribing sacubitril/valsartan in circumstances where therapy had been commenced by a medical practitioner, but a stable dose had yet to be achieved. The Committee reaffirmed that initiating treatment should continue to be restricted to medical practitioners. The PBAC considered it was reasonable to include an additional administrative note in the restriction clarifying that continuing therapy only provisions for nurse practitioners are intended to include any dose titration patients may require. How such clarification is expressed in the PBS listing would be left to the Secretariat to determine.

7.8 While the PBAC considered there may be a clinical place for sacubitril/valsartan in an expanded heart failure with reduced ejection fraction (HFrEF) population, the submission did not provide sufficient information to make a determination about the comparative effectiveness or cost effectiveness versus the current treatment options for these populations.

7.9 The PBAC considered that overall the comparative benefits and harms were difficult to assess due to the lack of data, however considered that sacubitril/valsartan may be of similar overall effectiveness and safety (but not cost effectiveness) to its current listings when used in either the LVEF 41% - ≤50% or ACE inhibitor/ARB-naïve populations.

7.10 The PBAC did not accept the reasoning in the submission that an economic analysis was not necessary. The proposition that established cost effectiveness in the ACE

inhibitor/ARB experienced LVEF ≤40% population could be extended to the LVEF 41% - ≤50% and treatment naïve populations without a formal economic analysis was unreasonable and inappropriate.

7.11 The PBAC agreed with the DUSC that the utilisation estimates were highly uncertain and considered the request would likely substantially expand the population who would be eligible for sacubitril/valsartan. In particular, the PBAC shared the concerns of the DUSC that the expanded population would include patients with less severe disease who may have preserved ejection fraction (HFpEF) who would receive no incremental benefit from sacubitril/valsartan over substantially less costly ACE inhibitors or ARBs. Furthermore, the PBAC agreed with the DUSC that the methodology used to estimate use and uptake in the expanded population, which was based on use of sacubitril/valsartan in the LVEF ≤40%, post-ACE inhibitor/ARB population was unlikely to be reliable.

7.12 The PBAC reiterated that any resubmission should be a major resubmission that includes all of the standard components expected for a major submission and addresses the following:

- For the LVEF 41% - ≤50% population, the PBAC considered that as the Sponsor has indicated no additional data will be forthcoming or made available, that a resubmission for this population would require a formal economic analysis which could be either:
    - A modelled cost effectiveness analysis for the LVEF 41% - ≤50% population, that may be in a subpopulation of that group such as in patients who have been hospitalised for heart failure or were still symptomatic (NYHA Class II-IV); or
    - a clinical claim of non-inferiority to ACE inhibitors/ARBs and a cost minimisation analysis versus these agents.
- For use in ACE inhibitor/ARB naïve patients (i.e. first line use), any resubmission for this population should include a formal economic analysis:
    - If a claim of superior comparative efficacy and/or safety is made over ACE inhibitors/ARBs for first line treatment, a modelled cost effectiveness analysis would be required; or
    - If a claim of non-inferior comparative efficacy and/or safety to ACE inhibitors/ARBs is made, a cost minimisation analysis versus these agents would be reasonable.

7.13 The PBAC noted that this submission is eligible for an Independent Review.

Outcome(s):

Amend listing to allow use in left ventricular ejection fraction (LVEF) 41% - ≤50% and ACE inhibitor/ARB naïve (i.e. first line use) populations:

Rejected

Amend listing to allow greater flexibility for beta blocker use/dosing and nurse practitioner prescribing in the titration phase:

Recommended

8 Recommended listing

8.1 Amend existing listing as follows:

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Available brands
SACUBITRIL with VALSARTAN					
sacubitril 24.3 mg + valsartan 25.7 mg tablet, 56	11123K	1	56	5	Entresto
sacubitril 48.6 mg + valsartan 51.4 mg tablet, 56	11131W	1	56	5	Entresto
sacubitril 97.2 mg + valsartan 102.8 mg tablet, 56	11122J	1	56	5	Entresto

Amend Restriction Summary 6915 / Treatment of Concept: 6915	
	Category / Program: GENERAL – General Schedule (Code GE)
	Prescriber type: ☒Medical Practitioners ☒Nurse practitioners - CTO
	Restriction Type: ☒Authority Required – Streamlined [6915]
	Indication: Chronic heart failure
	Clinical criteria:
	Patient must be symptomatic with NYHA classes II, III or IV
	AND
	Clinical criteria:
	Patient must have a documented left ventricular ejection fraction (LVEF) of less than or equal to 40%
	AND
	Clinical criteria:
	Patient must receive concomitant optimal standard chronic heart failure treatment**,** *which should include a beta-blocker, unless contra-indicated or not tolerated* ~~which must include the maximum tolerated dose of a beta-blocker, unless contraindicated or not tolerated,~~
	AND
	Clinical criteria:
	Patient must have been stabilised on an ACE inhibitor at the time of initiation with this drug, unless such treatment is contraindicated according to the TGA-approved Product Information or cannot be tolerated; or
	Patient must have been stabilised on an angiotensin II antagonist at the time of initiation with this drug, unless such treatment is contraindicated according to the TGA-approved Product Information or cannot be tolerated
	AND
	Clinical criteria:
	The treatment must not be co-administered with an ACE inhibitor or an angiotensin II antagonist.
	Administrative Advice: **Continuing Therapy Only:** For prescribing by nurse practitioners as continuing therapy only, where the treatment of, and prescribing of medicine for, a patient has been initiated by a medical practitioner. Further information can be found in the Explanatory Notes for Nurse Practitioners.
	Administrative Advice: *Continuing therapy by a nurse practitioner may include dose titrations/changes, but only after therapy was initiated by a medical practitioner.*
	Administrative Advice: Special Pricing Arrangements apply.

These restrictions may be subject to further review. Should there be any changes made to the restriction the Sponsor will be informed.

9 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers

applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

10 Sponsor's Comment

Novartis is disappointed that the PBAC did not recommend changes to the PBS listing to include a broader patient population with HF. Novartis welcomes the amendments to beta blocker requirements in the restriction to be more consistent with clinical guidelines and allow greater flexibility for clinical decision making.

This PSD was subject to the new process and standardised redaction criteria which allows for the publication of clinical data that are not already in the public domain. Novartis Australia did not have approval for the publishing of any additional data for the pivotal trial other than that presented in the published papers at the time of the PBAC submission and during the evaluation process.